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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,255	06/07/2000	Charles J. Link JR.	P04091US1	8671

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/589,255	LINK	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment, the declaration under 37 CFR 1.132, and the terminal disclaimer received on 7/15/03 have been entered. New claims 35-39 have been entered. Claims 19-39 are currently pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code not included in this action can be found in the previous office action.

35 USC § 132

The objection under 35 U.S.C. 132 to the new matter introduced by the amendment filed on 11/19/02 is withdrawn in view of the cancellation of the new matter.

The amendment filed 7/15/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the applicant has amended the claims 19-31 and 36-38 to recite "activating a hyperacute rejection in the subject in the absence of gene transfer", or "inhibiting the growth of the tumor in the subject in the absence of gene transfer", or "attacking said tumor in the absence of gene transfer", the specification does not support the phrase "in the absence of gene

transfer". The applicant is invited to specifically point out by page and line number where in the specification support for this terminology can be found.

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 112

The rejection of claims 19-34 under 35 U.S.C. 112, first paragraph, for lack of written description for "non-gene therapy-based" methods is withdrawn in view of applicant's cancellation of the this terminology in the claims as amended. However, please note that amended claims 19-31 are subject to new grounds of rejection under 35 U.S.C. 112, first and second paragraphs, see below.

Claims 19-31, and 36-38 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's new claims 19-31 and 36-38 introduce new matter into the disclosure of the specification by reciting methods "in the absence of gene transfer" which are not supported by the specification, see also above under 35 U.S.C. 132. The specification does not define what is meant by method of treating cancer " in the absence of gene transfer", or provide any example or description of such methods, see also below under 35 U.S.C. 112, second paragraph. The specification teaches the treatment of tumors by the

administration of murine retroviral producer cell lines wherein the retrovirus encodes a gene, HSV-TK. Since the methods disclosed in the specification include the administration of a gene, the specification does not appear to support a methods of treating cancer "in the absence of gene transfer". The applicant is invited to specifically point out where in the specification support for this terminology and subject matter can be found.

The rejection of claims 19-34 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view of the declaratory evidence provided in the declaration by Charles Link under 37 CFR 1.132.

The rejection of claims 19-34 under 35 U.S.C. 112, second paragraph, for indefiniteness based on the recitation of a "non-gene therapy-based method" for inhibiting tumor growth, is withdrawn in view of applicant's amendments to the claims. However, please note that the amendments of the claims and addition of new claims 35-39 have resulted in new grounds of rejection of the claims under 35 U.S.C. 112, second paragraph, see below.

Claims 19-34, and 36-38 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended or new claims 19-31, and 36-38 recite "in the absence of gene transfer". The specification does not provide support for this limitation or provide a definition of "gene transfer". Since the detailed description of the invention discloses the use of retroviral producer cells or cells which have been modified to express HSV-TK or α (1,3) galactosyl transferase, it is unclear how the use of such cells would qualify as "in the absence of gene transfer", since the introduction of such cells would automatically introduce genes into the human subject. Likewise, even the use of non-transduced cells would introduce heterologous genes into the human subject. Therefore, in the absence of any recitation or description of methods "in the absence of gene transfer", or any definition of "in the absence of gene transfer", the metes and bounds of the claim cannot be determined.

Amended claims 32-34 lack antecedent basis for the limitation , "delivery to the tumor of the murine cell line". The claims as amended recite that the murine cell line is delivered to the peritoneal cavity and not to the tumor as previously recited. Therefore, there is no antecedent basis for this limitation. Furthermore, claims 32-34 as amended recite the limitation wherein, "tumor cells are destroyed prior to transduction of a HSV tk gene". The methods as claimed does not recite a step wherein and HSV tk gene is transduced. In addition, this limitation is confusing in that it is unclear what is the target of the HSV tk gene transduction. As such the metes and bounds of these claims cannot be determined.

Double Patenting

The rejection of original, amended or new claims 19-24, 26-29 and 35-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 7 of U.S. Patent No. 5,869,035, hereafter referred to as the '035 patent, is withdrawn in view of applicant's submission of a terminal disclaimer.

Claim Rejections - 35 USC § 102

The rejection of original amended, or new claims 19-24, 26-29, and 35-39 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,869,035, hereafter referred to as the '035 patent, is withdrawn in view of applicant's submission of a terminal disclaimer.

The rejection of claims 19-34 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,045,789, hereafter referred to as Culver et al., is withdrawn in view of applicant's arguments.

The rejection of record over original, amended, or new claims 19-39 under 35 U.S.C. 102(a) over Klatzmann et al. stands. Applicant's arguments have been fully considered but have

not been found persuasive in overcoming the instant grounds of rejection of reasons of record as discussed in detail below.

The applicant argues that the claimed methods are directed to immunotherapy of tumors by the administration of murine VPC (vector producer cells) proximal or distal to the tumor in the peritoneal cavity of the subject, and that applicant's methods induce hyperacute rejection without activation of HSV tk gene as taught by Klatzmann. The applicant states that Klatzmann teaches HSVtk/gancyclovir gene therapy of cancer and that applicant's immunotherapy effects are observed in the absence of gene transfer and with no administration of GCV. The applicant further argues that since Klatzmann did not recognize that hyperacute rejection can mediate tumor killing, Klatzmann cannot anticipate the instant claims under the principle of inherency.

In response, please note that the phrase "in the absence of gene transfer," has been objected to under 35 U.S.C. 132 and rejected under 35 U.S.C. 112, first and second paragraphs for new matter, lack of description, and indefiniteness. In addition, claims 19-34 and 36-38 either comprise or specifically recite the step of administering a chemotherapeutic agent, see the limitations of claims 25, 30, and 32-34 in particular. Thus, the arguments pertaining to the administration of gancyclovir do not apply to these claims. Furthermore, the office does not agree with the applicant's reading of the teachings of Klatzmann et al. As stated in the previous office actions, Klatzmann et al. teaches the treatment of metastatic melanoma in humans by direct intratumoral injection of a xenogeneic murine retroviral producing cell line that produces a retrovirus encoding HSV-TK followed 10 days later by the administration of ganciclovir

(Klatzmann et al., page 2585). The tumors are located in various locations including the trunk, liver, and retroperitoneum. While it is true that Klatzmann et al. was interested in the effects of HSV-TK expression and gancyclovir on tumor growth, Klatzmann in fact reported no actual HSV TK gene transfer in the majority of patients, see Table 3. For patients who did demonstrate HSV-TK expression, Klatzmann et al. teaches that the transduction of the patient's tumor cells was less than 1%. This is an identical result to that observed by applicants after murine VPC encoding HSV-TK were administered, see the specification, page 27, lines 15-17. Furthermore, Klatzmann et al. reported a decrease in tumor volume **before** administration of GCV, see Figure 2. Based on the results obtained, Klatzmann et al. therefore postulated that the observed clinical effects of VPC treatment were, ".. due to the immunological consequences of injecting murine cells, and not to transgene transduction" (Klatzmann et al, page 2593, column 1, paragraph 1). Thus, Klatzmann's results actually demonstrate treatment of tumors by intratumoral injection of murine VPCs in the absence of gene transfer or gancyclovir treatment.

Furthermore, the murine VPCs used by Klatzmann et al. appear to be similar to those used by the applicant. Regarding inherency, the previous office action stated that while Klatzmann et al. does not explicitly teach that the murine retroviral producer cells express α(1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α(1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α(1,3) galactosyl epitopes. The MPEP states that "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re*

Best, 195 USPQ 430, 433 (CCPA 1997). In other words, there is no requirement that Klatzmann et al. recognized all the potential properties of the murine VPCs. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989), and *In re Spada*, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990). The applicant has not provided any evidence that the murine VPCs used by Klatzmann et al. do not meet the claim limitations or are functionally different than those taught by applicants. Regarding applicant's argument that Klatzmann et al. does not specifically teach hyperacute rejection, the previous paragraph pointed out that Klatzmann et al. did in fact speculate that immunological reactions of the human subjects to the murine VPC were in fact responsible for the clinical observations. However, assuming arguendo that Klatzmann et al. does not teach hyperacute immune responses, case law is clear that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. See *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Klatzmann et al. teaches the same method steps as those recited in the claims, and further teaches the use of the same VPCs as disclosed by applicants.

Finally, regarding applicant's argument that Klatzmann et al. teaches away from the instant invention by suggesting methods of improving murine packaging cell survival, the fact that Klatzmann et al. offers suggestions for increasing transgene expression does not invalidate the key teaching of the reference, which is the administration of murine VPCs to a human host to treat cancer. Furthermore, Klatzmann et al. concludes that the clinical trial involving the intratumoral administration of murine VPCs to humans indicates good tolerance and potential efficacy of this treatment modality for cancer therapy (Klatzmann et al., page 2593, column 1, last paragraph). In fact the authors were so encouraged by their results and particularly the observed immunological effects that they suggest further reinforcing the immune response by combining the VPC therapy with cytokines (Klatzmann et al., page 2593, column 1, last paragraph).

Thus, for the reasons discussed above and in previous office actions, applicant's arguments do no overcome the instant rejection. The rejection of record is therefore maintained.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Dr. A.M.S. Wehbé

ANNE M. WEHBÉ, PH.D.
PRIMARY EXAMINER